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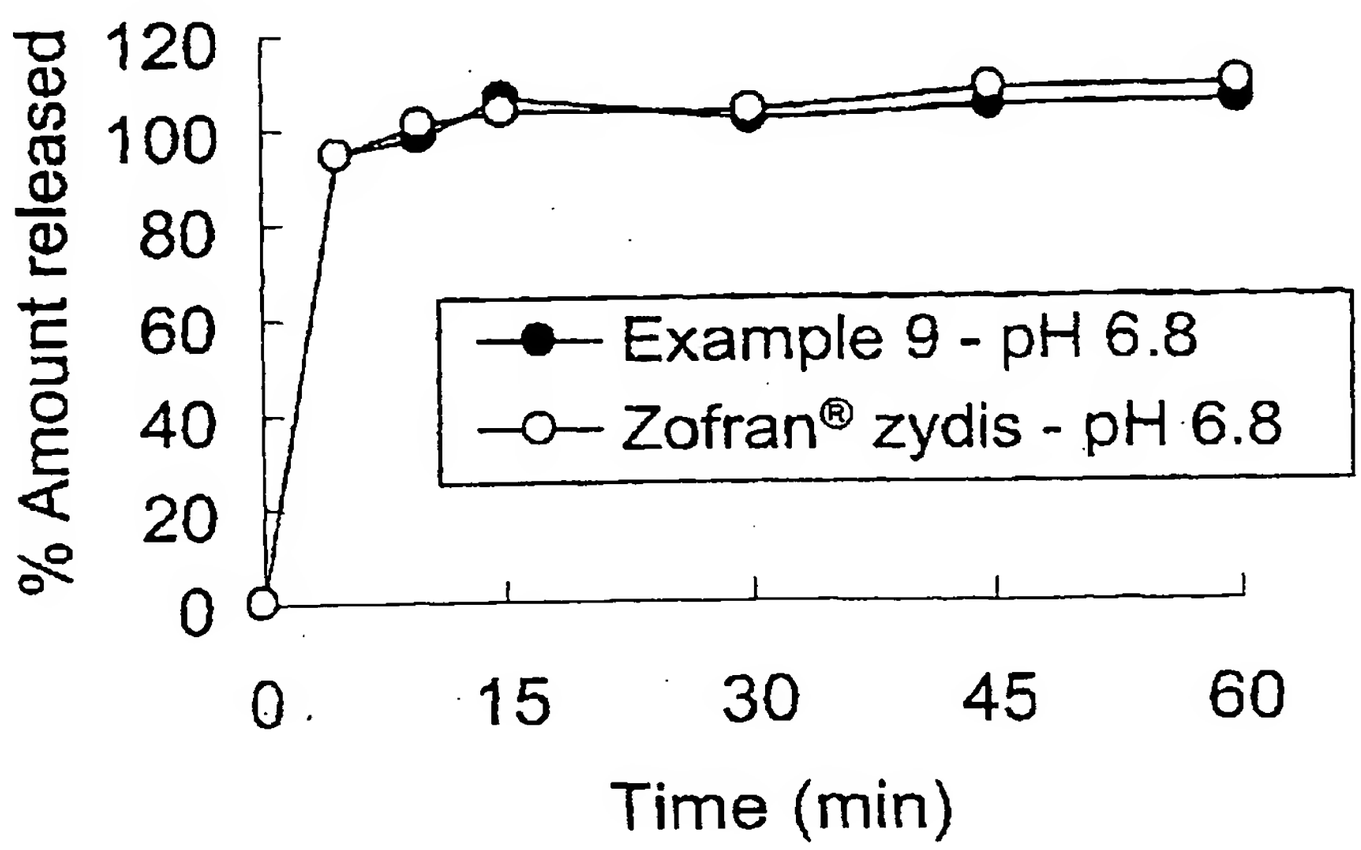

(57) Abstract: A tablet having an enhanced strength as well as a high disintegrating rate in the oral cavity is prepared by mixing an active ingredient, a sublimable substance suitable for oral administration and a pharmaceutically acceptable additive; tableting the mixture; and drying the resulting tablet to sublime the sublimable substance until the tablet becomes porous.

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RAPIDLY DISINTEGRATING TABLET AND PROCESS FOR THE MANUFACTURE THEREOF

Field of the Invention

The present invention relates to a rapidly disintegrating tablet for oral administration which has an enhanced strength as well as a high disintegrating rate in the oral cavity, and a process for the manufacture thereof.

Background of the Invention

Preparations for oral administration normally come in the form of tablet, granule, powder or solution. Since a solid preparation need be swallowed with some water, a liquid preparation is normally preferred by the elderly, infants or patients who have difficulty in swallowing. In spite of such advantage, a liquid preparation has shortcomings in that it is difficult to handle, especially in measuring an accurate dosage, and that it is not suitable for drugs which are unstable in a moist environment. Therefore, efforts have been made to develop a rapidly disintegrating tablet which easily disintegrates by the action of saliva.

There have been commercialized rapidly disintegrating tablets prepared by lyophilizing solutions containing various drugs(US Patent Nos. 5,631,023 and 5,976,577), e.g., Pepcid® RPD(famotidine preparation, Merck) and Zofran® zydis(ondansetron preparation, Glaxo wellcome), Claritin® RediTabs(loratadine preparation, Schering). However, these tablets have the disadvantage in that the productivity of the process for the preparation thereof is very low because the process involves the steps of injecting a drug solution into a pre-formed container, lyophilizing and coating the lyophilized product with an expensive material.

Instead of lyophilization, Yamanouch Pharmaceutical Co. Ltd. has disclosed in WO 99/47126 a rapidly disintegrating tablet prepared by using a water-soluble non-saccharide polymer as a binder together with an active ingredient; and humidifying the tablet. Further, WO 93/12769 discloses a rapidly disintegrating tablet prepared by filling a mold with a suspension containing an active ingredient together with agar and sugar; and drying the suspension to remove the solvent at 30 ℃ in a vacuum. However, these

processes suffer from low productivity and uneven product quality.

Cima Labs has developed Orasolv technique which is disclosed in US Patent Nos. 5,173,878 and 6,024,981. Among the tablets prepared thereby, Zomig® Rapimelt(zolmitriptan preparation, Astrazeneca) has been commercialized. This tablet contains an effervescent substance but has the problems of incomplete disintegration in the oral cavity and the displeasing effect of the effervescent gas generated in the oral cavity.

US Patent No. 3,885,026 discloses porous tablets prepared by adding a volatilizable adjuvant, e.g., urethane, urea, ammonium carbonate or naphthalene, to other tablet components; tableting the resulting mixture; and heating the tablets to volatilize the adjuvant. However, a residual amount of the adjuvant in the tablet may generate a deleterious effect on the patient.

US Patent No. 4,134,943 discloses porous tablets prepared by adding a liquid having a freezing temperature in the range of –30 to 25 ℃ to other tablet components; cooling the mixture below the freezing temperature to solidify the liquid; tableting the cooled mixture; and then evaporating the liquid. However, this process suffers from low productivity.

Summary of the Invention

Accordingly, it is an object of the present invention to provide an improved process for preparing a rapidly disintegrating tablet which can be handled easily.

It is another object of the present invention to provide a rapidly disintegrating tablet prepared by said process.

In accordance with one aspect of the present invention, there is provided a process for preparing a rapidly disintegrating tablet which comprises the steps of: mixing an active ingredient, a sublimable substance which is allowable for oral administration, and a pharmaceutically acceptable additive; tableting the mixture; and drying the resulting tablet to sublime the sublimable substance until the tablet becomes porous.

Brief Description of the Drawings

The above objects and features of the present invention will become apparent from the following description of preferred embodiments taken in conjunction with the accompanying drawings, in which:

Figs. 1A to 1D show *in vitro* release profiles of the inventive tablet and Zofran® zydis at pH 1.2, 4.0, 6.8, and water, respectively.

Detailed Description of the Invention

A composition which is used in preparation of the tablet of the present invention comprises an active ingredient, a sublimable substance which is allowable for oral administration, and a pharmaceutically acceptable additive such as saccharide, binder, surfactant, poly(ethylene glycol), excipient and lubricant.

(1) Active ingredient

The active ingredient which may be used in the tablet of the present invention include any pharmacologically active ingredients which can be orally administered, and preferred are those which dissolve rapidly in the oral cavity, the examples thereof being listed below:

① Antifebrile, analgesic or anti-inflammatory agents, e.g., aspirin, acetaminophen, indomethacin, sodium diclofenac, ketoprofen, isopropyl antipyrine, phenacetin, flurbiprofen and phenyl butazone;

② Anti-gastric ulcer agents, e.g., cimetidine, famotidine, ranitidine and nizatidine;

③ Cardiovascular agents or vasodilants, e.g., nifedipine, almodipine, verapamil, captopril, diltiazem HCl, propranolol, oxprenolol, nitroglycerin and enalapril maleate;

④ Antibiotics, e.g., cephalosporins such as ampicillin, amoxicillin and cephalexin; erythromycin; tetracycline; and quinolones;

⑤ Antitussives or antiasthmatics, e.g., theophylline, aminophylline, codeine phosphate, methylephedrine HCl, dextromethorphan, noscapine, salbutamol, ambroxol, clenbuterol and terbutaline;

⑥ Antiemetics or stomach function-regulating agents; e.g., ondansetron, metoclopyramide, domperidone, trimebutine maleate, cisapride and levosulpiride;

⑦ Impotence-treating agents, e.g., agents that block the cleavage of nitrogen monoxide, including sildenafil, preferably a water soluble salt thereof; and

⑧ Others which include a migrain-treating agent such as zolmitriptan and rizatriptan; a psychostimulant; an antibacterial agent; an antihistamines

such as loratadine; antidiabetic; an allergy-treating agent; a contraceptive; a vitamin; an anticoagulant; a muscle-relaxing agent; a cerebral metabolism-improving agent; an antidiuretic; an anticonvulsant; and a Parkinson disease-treating agent such as selegiline.

The active ingredient may be used in an amount of 0.5 to 80 % by weight, preferably 1 to 70 % by weight, based on the weight of the composition.

(2) Sublimable substance

The sublimable substance which may be used in the present invention is a substance that causes no harmful effects when administered orally. The sublimable substance is tableted together with an active ingredient and pharmaceutically acceptable additives and then the resulting tablet is dried. During the drying process, the sublimable substance is sublimed to generate pores in the tablet. The porous tablet so obtained easily disintegrates in the oral cavity.

To accomplish such effect, the sublimable substance has to be sublimed at a temperature ranging from 40 to 60 ℃, preferably 40 to 50 ℃, more preferably 42 to 48 ℃, to prevent any property change of the saccharide. Further, since a residual amount of the substance may remain in the tablet after the drying process, it should not have a bad taste in addition to the requirement of being harmless. In the drying process, a reduced pressure may be employed in order to enhance the sublimation.

Representative sublimable substances which may be suitably used in the present invention include menthol; camphor; thymol; an organic acid such as adipic acid; and a lower fatty acid, e.g., arachidic acid, capric acid, myristic acid and palmitic acid, and a mixture thereof: and, among these, menthol is preferred.

The sublimable substance may be used in an amount of 5 to 50 % by weight, preferably 10 to 40 % by weight, based on the weight of the composition.

(3) Saccharide

A saccharide having a sweet taste and good solubility in water may be used in the present invention. Representative saccharides include lactose, mannitol, sorbitol, xylitol, erythritol, glucose, sucrose, fructose, rebulose, maltodextrin, paratinose, and a mixture thereof. Preferred are spray-dried, porous particulates thereof which are highly soluble in the oral cavity. The

saccharide may be used in an amount of 10 to 95 % by weight, preferably 20 to 90 % by weight, based on the weight of the composition.

(4) Binder

The binder gives the tablet the strength necessary for good handling and storage stability. Representative binders include polyvinylpyrrolidone, a copolymer of vinylpyrrolidone and vinylacetate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, arabia gum, tragacanth gum, xanthan gum, sodium alginate, pectin, agar, water-dispersible starch and derivatives thereof, and a mixture thereof.

The binder may be used in an amount of 0.1 to 15 % by weight, preferably 1 to 10 % by weight, based on the weight of the composition.

(5) Surfactant

The surfactant may be used as a dissolution-supplementing agent in the composition. Representative surfactants include polyoxyethylene glycolated natural or hydrogenated vegetable oils such as Cremophor®(BASF); polyoxyethylene-sorbitan fatty acid ester such as Tween®(ICI); polyoxyethylene-polyoxypropylene block copolymer such as Poloxamer®(BASF); sorbitan fatty acid ester such as Span®(ICI); sodium lauryl sulfate; phospholipid and a mixture thereof. The surfactant may be used in an amount of 0.2 to 5 % by weight, preferably 0.3 to 3.0 % by weight, based on the composition.

(6) Poly(ethylene glycol)

A poly(ethylene glycol) may be used in the present invention to enhance the drug dissolution and abrasion resistance of the tablet. Preferred are those having a weight average molecular weight ranging from 1,000 to 20,000 preferably 1,500 to 10,000. The poly(ethylene glycol) may be used in an amount of 1 to 15 % by weight, preferably 2 to 10 % by weight, based on the weight of the composition.

(7) Others

In addition to the saccharide, binder, surfactant and poly(ethylene glycol), the pharmaceutically acceptable additives which may be used in the present invention further include a disintegrator, e.g., cross-linked polyvinylpyrrolidone, sodium starch glycolate or calcium carboxymethyl

cellulose; a lubricant, e.g., magnesium stearate, talc, silica, sodium stearyl fumarate or valine; a sweetening agent, e.g., aspartame, stevioside; an excipient, e.g., microcrystalline cellulose; an inorganic substance, e.g., silicon dioxide, hydrotalcite, aluminum magnesium silicate, aluminum hydroxide, titanium dioxide, aluminum silicate, magnesium aluminum metasilicate or bentonite; and a mixture thereof. Each additive may be used in an amount of 0.1 to 20 % by weight, preferably 0.2 to 10 % by weight, based on the weight of the composition.

Among these ingredients, the active ingredient or saccharide may be used in the form of spray-dried particulate. The term "particulate" as used in the present invention means a substance comprised of particles of any shape.

A particulate containing an active ingredient may be obtained by dissolving the active ingredient in an appropriate solvent, e.g., water, ethanol or methanol, and drying the resulting solution using a conventional spray drying method. The active ingredient particulate may further contain an additive such as a binder, an inorganic substance or a mixture thereof. In such a case, the active ingredient and the additive may be used in a weight ratio ranging from 1:0.1 to 1:10, preferably 1:0.3 to 1:3. The amount of active ingredient particulate used in preparing the inventive composition may be adjusted so that the content of the active ingredient falls within the range described previously. When the active ingredient particulate contains a binder, an inorganic substance or a mixture thereof, the active ingredient in the composition becomes more readily soluble and the taste of the drug can be blocked. Therefore, such a particulate is suitable for a drug having a poor solubility in water or bitter taste. The active ingredient particulate may be preferably combined with a sublimable substance and a poly(ethylene glycol) in the composition.

A particulate containing a saccharide may be obtained by dissolving a saccharide in an appropriate solvent, e.g., water, and drying the resulting solution using a conventional spray drying method. The saccharide particulate may further contain an additive such as a binder, a surfactant or a mixture thereof. In such a case, the saccharide and the additive may be used in a weight ratio ranging from 1:0.01 to 1:0.5, preferably 1:0.02 to 1:0.2. The amount of the saccharide particulate used in preparing the inventive composition may be adjusted so that the saccharide content falls with the range described previously. When such a saccharide particulate is employed in the preparation of the tablet, the tablet attains an improved solubility of the active ingredient due to the particulate's pores. Further, when the saccharide

particulate contains a binder, a surfactant or a mixture thereof, the tablet prepared therewith has an improved strength and gives smooth tactile sensation during its disintegration in the oral cavity.

The tablet of the present invention is prepared by mixing an active ingredient or a spray-dried particulate thereof, a sublimable substance which is allowable for oral administration, and pharmaceutically acceptable additives; tableting the mixture; and drying the resulting tablet at a temperature ranging from 40 to 60 ℃, preferably 40 to 50 ℃, more preferably 42 to 48 ℃.

The following Examples are intended to further illustrate the present invention without limiting its scope.

Example 1

Ingredients	Amount(㎎/tablet)
Ondansetron	4
Menthol	50
Mannitol	31
Tween® 80	0.9
Xylitol	100
Poly(ethylene glycol) 3000	7
Polyvinylpyrrolidone	3.5
Aspartame	3
Magnesium Stearate	2
Silicon dioxide	1
Talc	1
Sodium stearyl fumarate	6

Mannitol, polyvinylpyrrolidone and Tween® 80 were dissolved in water and the solution was subjected to spray drying to obtain a particulate material. The particulate was mixed with the remaining ingredients and the resulting mixture was tableted. The resulting tablet was dried at 45 ℃ for 24 hours to sublime menthol until the content of residual menthol became 1 ㎎ or less, to obtain a rapidly disintegrating tablet.

The fracture strength of the tablet was measured by applying a force(in g) against the tablet in the diametric direction using a loading plunger(diameter 1 ㎝) moving at a velocity of 0.5 ㎜/sec, and the force need to fracture the tablet(fracture strength) was observed to be approximately 130 g.

The abrasion resistance of the tablet was determined by tumbling 10 tablets at 25 rpm for 4 minutes in an abrasion tester(Erweka TA20) and then measuring the weight of each tablet. The resulting abrasive degree was 0.3%.

The disintegration time of the tablet in the oral cavity was determined by placing a tablet in a human mouth; and measuring the time period taken for complete disintegration of the tablet by saliva. This procedure was repeated 5 times using 5 separate individuals and a mean disintegration time was calculated from 3 data points omitting the longest and shortest time values. The resulting disintegration time was 10 seconds.

Example 2

Ingredients	Amount(mg/tablet)
Ondansetron	4
Menthol	40
Mannitol	70
Xylitol	60
Lactose	20
Polyvinylpyrrolidone	6
Magnesium Stearate	1
Silicon dioxide	1

Using the above ingredients, the procedure of Example 1 was repeated except that mannitol and polyvinylpyrrolidone were used in the preparation of the particulate, to obtain a rapidly disintegrating tablet.

The fracture strength of the tablet was approximately 120 g and the disintegrating time of the tablet in the oral cavity was approximately 15 seconds.

Example 3

Ingredients	Amount(mg/tablet)
Ondansetron	4
Menthol	40
Tween® 80	2
Mannitol	70
Xylitol	60

Lactose	20
Polyvinylpyrrolidone	9
Magnesium Stearate	1
Silicon dioxide	1

Using the above ingredients, the procedure of Example 1 was repeated, to obtain a rapidly disintegrating tablet.

The fracture strength of the tablet was approximately 300 g and the disintegrating time of the tablet in the oral cavity was approximately 20 seconds.

Example 4

Ingredients	Amount(mg/tablet)
Famotidine	20
Mannitol	70
Menthol	50
Sorbitol	70
Xylitol	60
Lactose	20
Polyvinylpyrrolidone	9
Magnesium Stearate	1
Silicon dioxide	1

Using the above ingredients, the procedure of Example 1 was repeated except that mannitol and polyvinylpyrrolidone were used in the preparation of the particulate, to obtain a rapidly disintegrating tablet.

The fracture strength of the tablet was approximately 140 g and the disintegrating time of the tablet in the oral cavity was approximately 20 seconds.

Example 5

Ingredients	Amount(mg/tablet)
loratadine	10
Mannitol	70
Menthol	40

Sorbitol	70
Lactose	70
Polyvinylpyrrolidone	14
Magnesium Stearate	1
Silicon dioxide	1

Using the above ingredients, the procedure of Example 1 was repeated except that mannitol and polyvinylpyrrolidone were used in the preparation of the particulate, to obtain a rapidly disintegrating tablet.

The fracture strength of the tablet was approximately 250 g and the disintegrating time of the tablet in the oral cavity was approximately 30 seconds.

Example 6

Ingredients	Amount(mg/tablet)
Rizatriptan	5
Menthol	50
Mannitol	71.7
Erythritol	50
Lactose	30
Polyvinylpyrrolidone	12
Magnesium Stearate	1
Silicon dioxide	1

Using the above ingredients, the procedure of Example 1 was repeated except that mannitol and polyvinylpyrrolidone were used in the preparation of the particulate, to obtain a rapidly disintegrating tablet.

The fracture strength of the tablet was approximately 250 g and the disintegrating time of the tablet in the oral cavity was approximately 25 seconds.

Example 7

Ingredients	Amount(mg/tablet)
Zolmitriptan	5
Menthol	60

Mannitol	71.7
Xylitol	60
Lactose	20
Polyvinylpyrrolidone	5
Magnesium Stearate	1
Silicon dioxide	1

Using the above ingredients, the procedure of Example 1 was repeated except that mannitol and polyvinylpyrrolidone were used in the preparation of the particulate, to obtain a rapidly disintegrating tablet.

The fracture strength of the tablet was approximately 80 g and the disintegrating time of the tablet in the oral cavity was approximately 5 seconds.

Example 8

Ingredients	Amount(mg/tablet)
Acetaminophen	100
Menthol	100
Mannitol	200
Xylitol	100
Lactose	50
Polyvinylpyrrolidone	15
Magnesium Stearate	2
Silicon dioxide	3

Using the above ingredients, the procedure of Example 1 was repeated except that mannitol and polyvinylpyrrolidone were used in the preparation of the particulate, to obtain a rapidly disintegrating tablet.

The fracture strength of the tablet was approximately 150 g and the disintegrating time of the tablet in the oral cavity was approximately 20 seconds.

Example 9

Ingredients	Amount(mg/tablet)
Ondansetron	8
Menthol	27

Mannitol	104.4
Xylitol	100
Poly(ethylene glycol) 3000	5.5
Poly(ethylene glycol) 6000	4.0
Stevioside	5.5
Cross-linked polyvinylpyrrolidone	4
Magnesium Stearate	1.2
Silicon dioxide	0.65

Using the above ingredients, the procedure of Example 1 was repeated except that ondansetron was dissolved in methanol and the solution was subjected to spray drying in the preparation of the particulate, to obtain a rapidly disintegrating tablet.

The fracture strength of the tablet was approximately 220 g and the disintegrating time of the tablet in the oral cavity was approximately 25 seconds.

Example 10

Ingredients	Amount(mg/tablet)
Ondansetron	8
Xanthan gum	6
Menthol	29
Mannitol	104.4
Polyethylene glycol 3000	9.5
Stevioside	5.5
Cross-linked polyvinylpyrrolidone	4
Magnesium Stearate	1.2
Silicon dioxide	0.65

Using the above ingredients, the procedure of Example 1 was repeated except that ondansetron and xanthan gum were dissolved in 50 % methanol and the solution was subjected to spray drying in the preparation of the particulate, to obtain a rapidly disintegrating tablet.

The fracture strength of the tablet was approximately 220 g and the disintegrating time of the tablet in the oral cavity was approximately 25

seconds.

Example 11

The procedure of Example 1 was repeated except that the ingredients were simply mixed without the step of preparing the particulate, to obtain a porous tablet.

The fracture strength of the porous tablet was approximately 90 g, the abrasive degree of the porous tablet was 11 %, and the disintegrating time of the porous tablet in the oral cavity was approximately 25 seconds.

As compared with the table obtained in this Example, the tablet of Example 1 has a higher fracture strength, lower abrasive degree and shorter disintegrating time than that of this Example.

Test Example: Dissolution Test

A dissolution test was conducted for the tablets obtained in Example 9 and Zofran® zydis(Glaxo wellcome) as a control, in accordance with the dissolution test method described in Korean Pharmacopoeia by the Korea Food and Drug Administration(KFDA) under the conditions listed below:

Test apparatus: ERWEKA DT80(Erweka, Germany)

Analytical method: liquid chromatography

- column: Inertsil ODS-2(4.6 x 150 mm; GL Science, Japan)
- mobile phase: Acetonitrile: 0.02M KH_2PO_4 = 30:70
- flow rate: 1.0 ml/min.
- detector: UV 278 nm

Figs. 1A to 1D show *in vitro* release profiles of the inventive tablet and Zofran® zydis at pH 1.2, 4.0, 6.8, and water, respectively. As can be seen from Figs. 1A to 1D, the inventive tablet shows a dissolution rate comparable to the Zofran® zydis control.

While the subject invention has been described and illustrated with reference to the preferred embodiments only, it may be apparent to those skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope of the present invention which is defined in the appended claims.

What is claimed is :

1. A process for preparing a rapidly disintegrating tablet which comprises: mixing an active ingredient, a sublimable substance suitable for oral administration, and a pharmaceutically acceptable additive; tableting the mixture; and drying the resulting tablet to sublime the sublimable substance until the tablet becomes porous.

2. The process of claim 1, wherein the active ingredient is an analgesic selected from the group consisting of aspirin, acetaminophen, indomethacin, sodium diclofenac, ketoprofen, isopropyl antipyrine, phenacetin, flurbiprofen and phenyl butazone; an anti-gastric ulcer agent selected from the group consisting of cimetidine, famotidine, ranitidine and nizatidine; a cardiovascular agent selected from the group consisting of nifedipine, almodipine, verapamil, captopril, diltiazem HCl, propranolol, oxprenolol, nitroglycerin and enalapril maleate; an antibiotic selected from the group consisting of ampicillin, amoxicillin, cephalexin, erythromycin, tetracycline and quinolone; an antiasthmatic selected from the group consisting of theophylline, aminophylline, codeine phosphate, methylephedrine HCl, dextromethorphan, noscapine, salbutamol, ambroxol, clenbuterol and terbutaline; an antiemetic agent selected from the group consisting of ondansetron, metoclopyramide, domperidone, trimebutine maleate; a stomach function-regulating agent selected from the group consisting of cisapride and levosulpiride; an impotence-treating agent; a migrain-treating agent selected from the group consisting of zolmitriptan and rizatriptan; a psychostimulant; an antibacterial agent; an antihistamines; an antidiabetic; an allergy-treating agent; a contraceptive; a vitamin; an anticoagulant; a muscle-relaxing agent; a cerebral metabolism-improving agent; an antidiuretic; an anticonvulsant; or a Parkinson disease-treating agent.

3. The process of claim 1, wherein the sublimable substance is selected from the group consisting of menthol, camphor, thymol, an organic acid, a lower fatty acid and a mixture thereof.

4. The process of claim 1, wherein the pharmaceutically acceptable additive is selected from the group consisting of a saccharide, a binder, a surfactant, a poly(ethylene glycol), an excipient, a lubricant and a mixture

thereof.

5. The process of claim 4, wherein the saccharide is lactose, mannitol, sorbitol, xylitol, erythritol, glucose, sucrose, fructose, rebulose, maltodextrin, paratinose, or a mixture thereof.

6. The process of claim 4, wherein the binder is polyvinylpyrrolidone, a copolymer of vinylpyrrolidone and vinylacetate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, arabia gum, tragacanth gum, xanthan gum, sodium alginate, pectin, agar, water-dispersible starch or its derivative, or a mixture thereof.

7. The process of claim 4, wherein the surfactant is a polyoxyethylene glycolated natural or hydrogenated vegetable oil, polyoxyethylene-sorbitan fatty acid ester, polyoxyethylene-polyoxypropylene block copolymer, sorbitan fatty acid ester, sodium lauryl sulfate, phospholipid or a mixture thereof.

8. The process of claim 4, wherein the poly(ethylene glycol) has a weight average molecular weight ranging from 1,000 to 20,000.

9. The process of claim 1, wherein the mixture contains 0.5 to 80 % by weight of the active ingredient and 5 to 50 % by weight of the sublimable substance.

10. . The process of claim 1, wherein the tableting step is conducted by directly tableting the mixture of the active ingredient, the sublimable substance suitable for oral administration, and the pharmaceutically acceptable additive.

11. The process of claim 1, wherein the pharmaceutically acceptable additive contains a poly(ethylene glycol), and the mixing step is conducted by dissolving the active ingredient in a solvent; spray drying the resulting solution to obtain a particulate; and mixing the particulate with the remaining ingredients containing the sublimable substance and the poly(ethylene glycol).

12. The process of claim 1, wherein the pharmaceutically acceptable

additive contains a poly(ethylene glycol) together with a binder, an inorganic substance or a mixture thereof, and the mixing step is conducted by dissolving the active ingredient together with the binder, the inorganic substance or the mixture thereof in a solvent; spray drying the resulting solution to obtain a particulate; and mixing the particulate with the remaining ingredients containing the sublimable substance and the poly(ethylene glycol).

13. The process of claim 12, wherein the active ingredient and, the binder, the inorganic substance or the mixture thereof are used in a weight ratio ranging from 1:0.1 to 1:10.

14. The process of claim 11 or 12, wherein the mixture contains 0.5 to 80 % by weight of the active ingredient in the particulate form.

15. The process of claim 1, wherein the pharmaceutically acceptable additive contains a saccharide, and the mixing step is conducted by dissolving the saccharide in a solvent; spray drying the resulting solution to obtain a particulate; and mixing the particulate with the remaining ingredients containing the active ingredient and the sublimable substance.

16. The process of claim 1, wherein the pharmaceutically acceptable additive contains a saccharide together with a binder, a surfactant or a mixture thereof, and the mixing step is conducted by dissolving the saccharide together with the binder, the surfactant or the mixture thereof in a solvent; spray drying the resulting solution to obtain a particulate; and mixing the particulate with the remaining ingredients containing the active ingredient and the sublimable substance.

17. The process of claim 16, wherein the saccharide and, the binder, the surfactant or the mixture thereof are used in a weight ratio ranging from 1:0.01 to 1:0.5.

18. The process of claim 15 or 16, wherein the mixture contains 10 to 95 % by weight of the saccharide in the particulate form.

19. The process of claim 1, wherein the drying step is conducted at a temperature ranging from 40 to 60 ℃.

20. A rapidly disintegrating tablet prepared by the process of any one of claims 1 to 19.

Fig. 1A

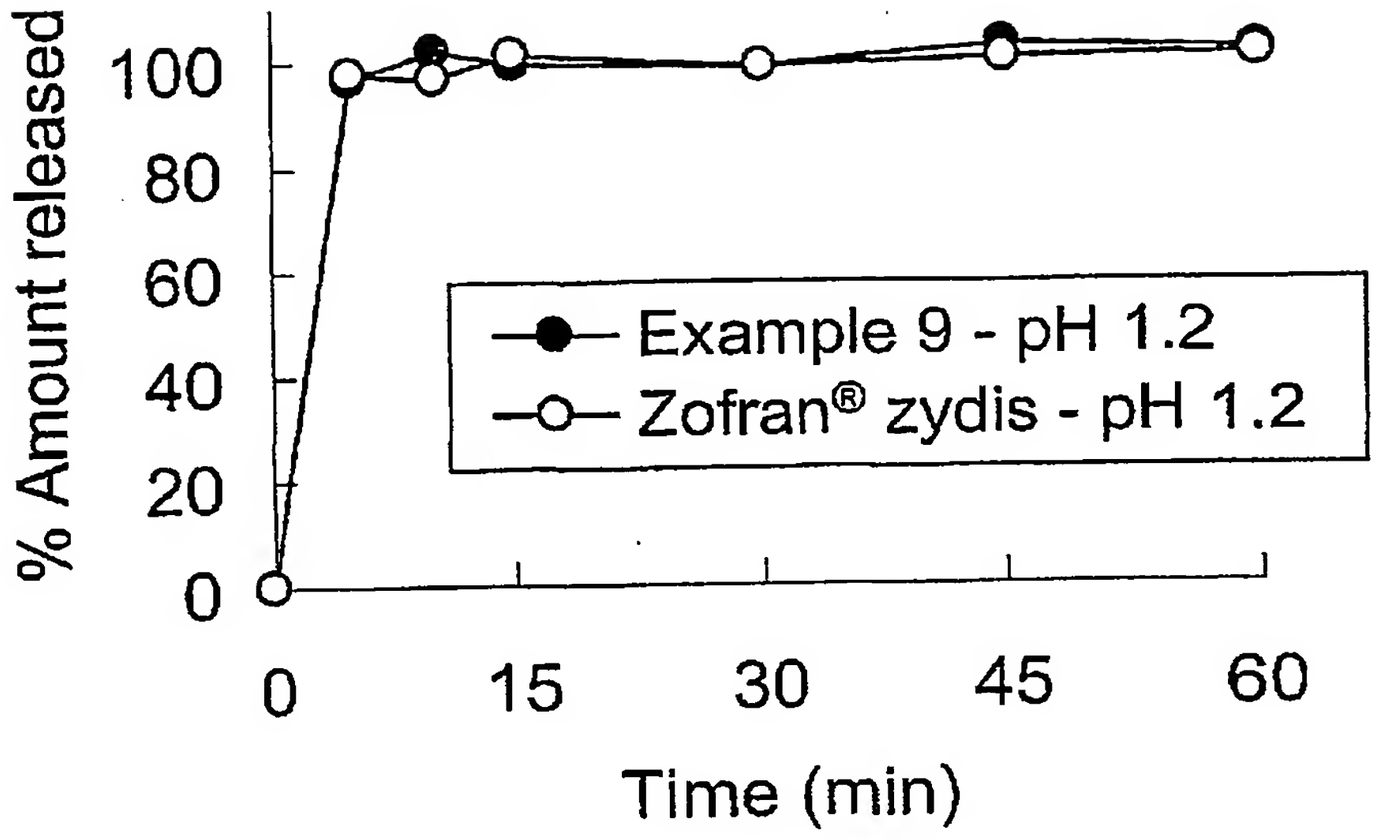
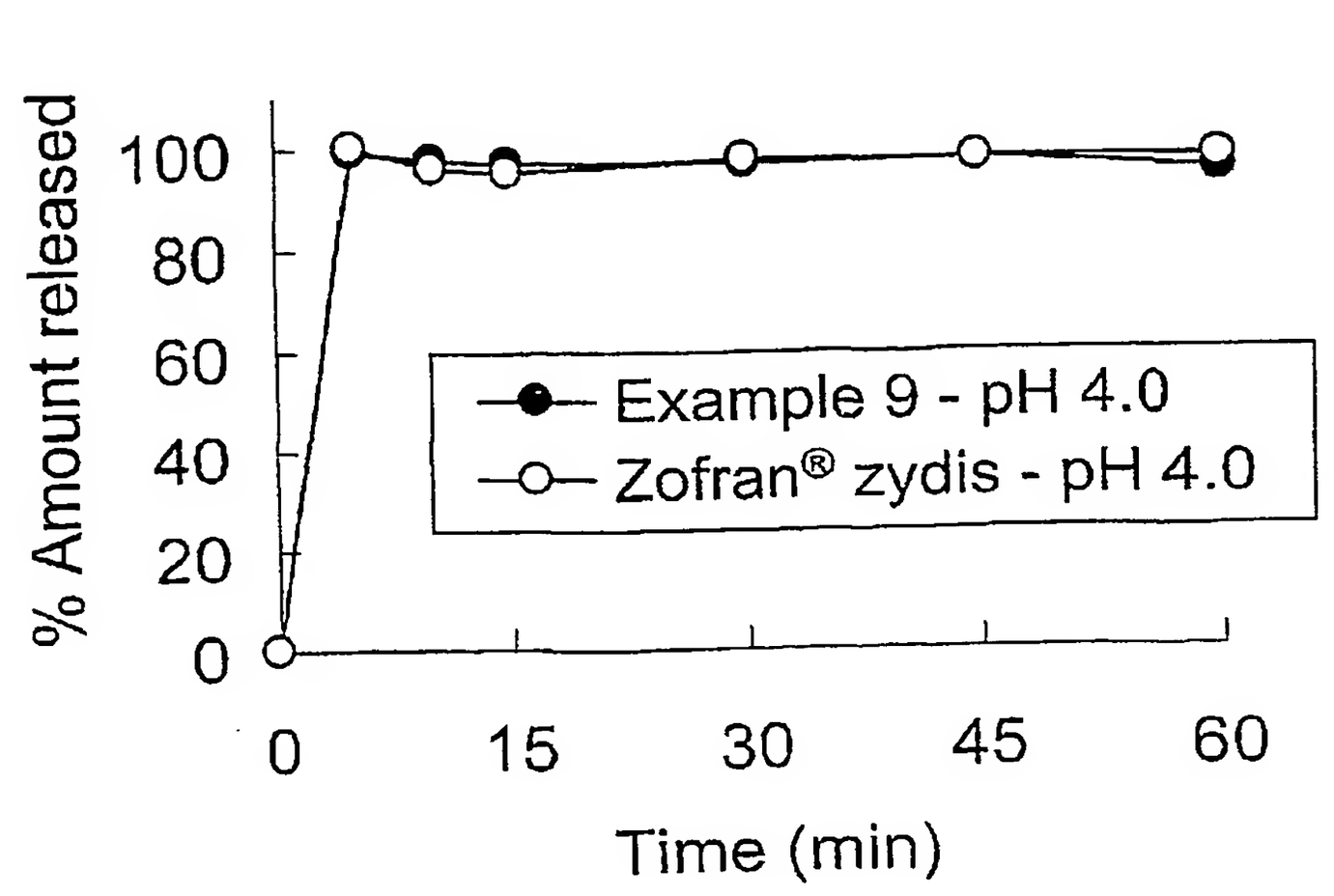

% Amount released
100
80
60
40
20
0
0
15
30
45
60
Time (min)
Example 9 - pH 1.2
Zofran® zydis - pH 1.2

Fig. 1B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100
80
60
40
20
0
0
15
30
45
60
Time (min)
Example 9 - pH 4.0
Zofran® zydis - pH 4.0

Fig. 1C

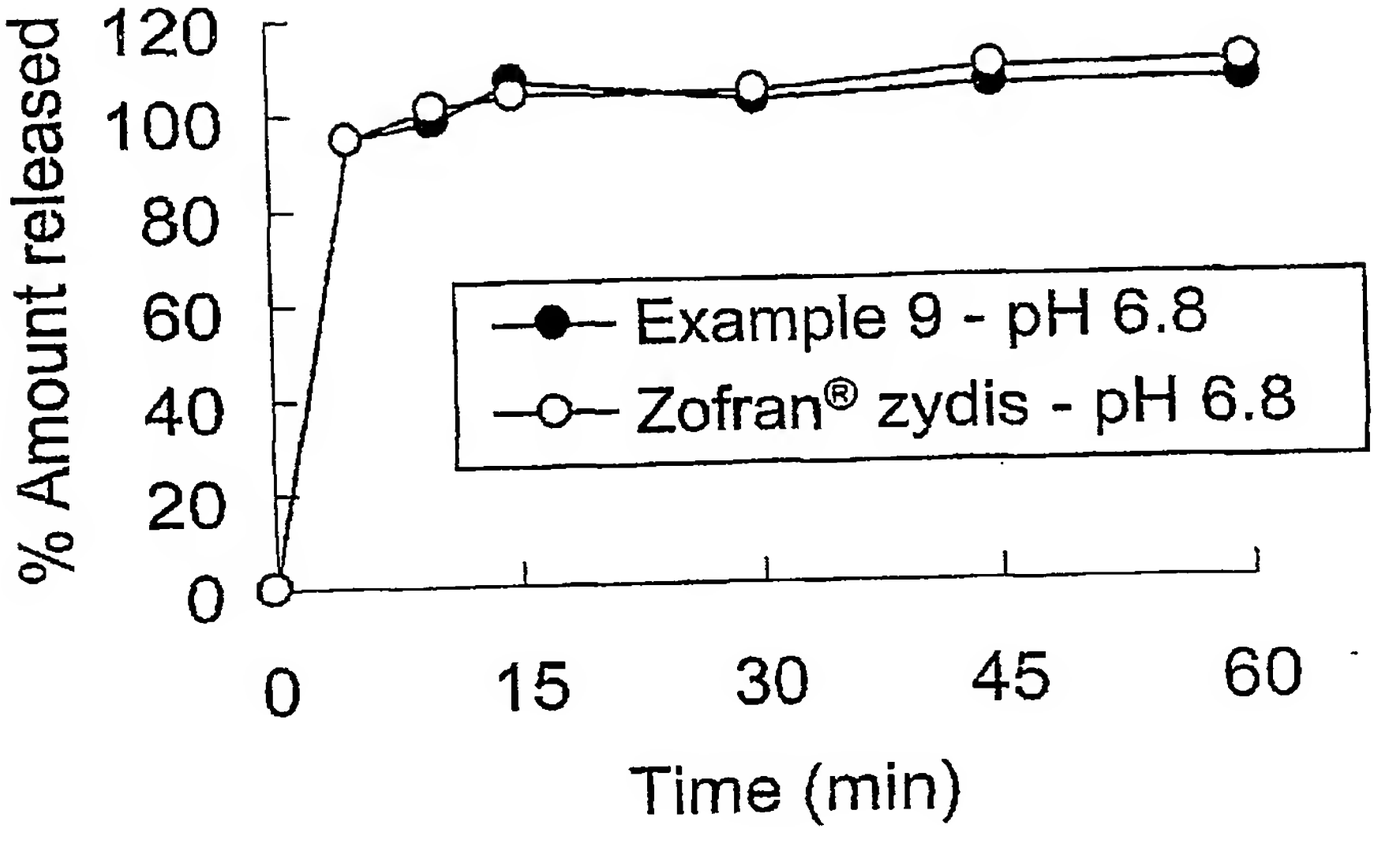
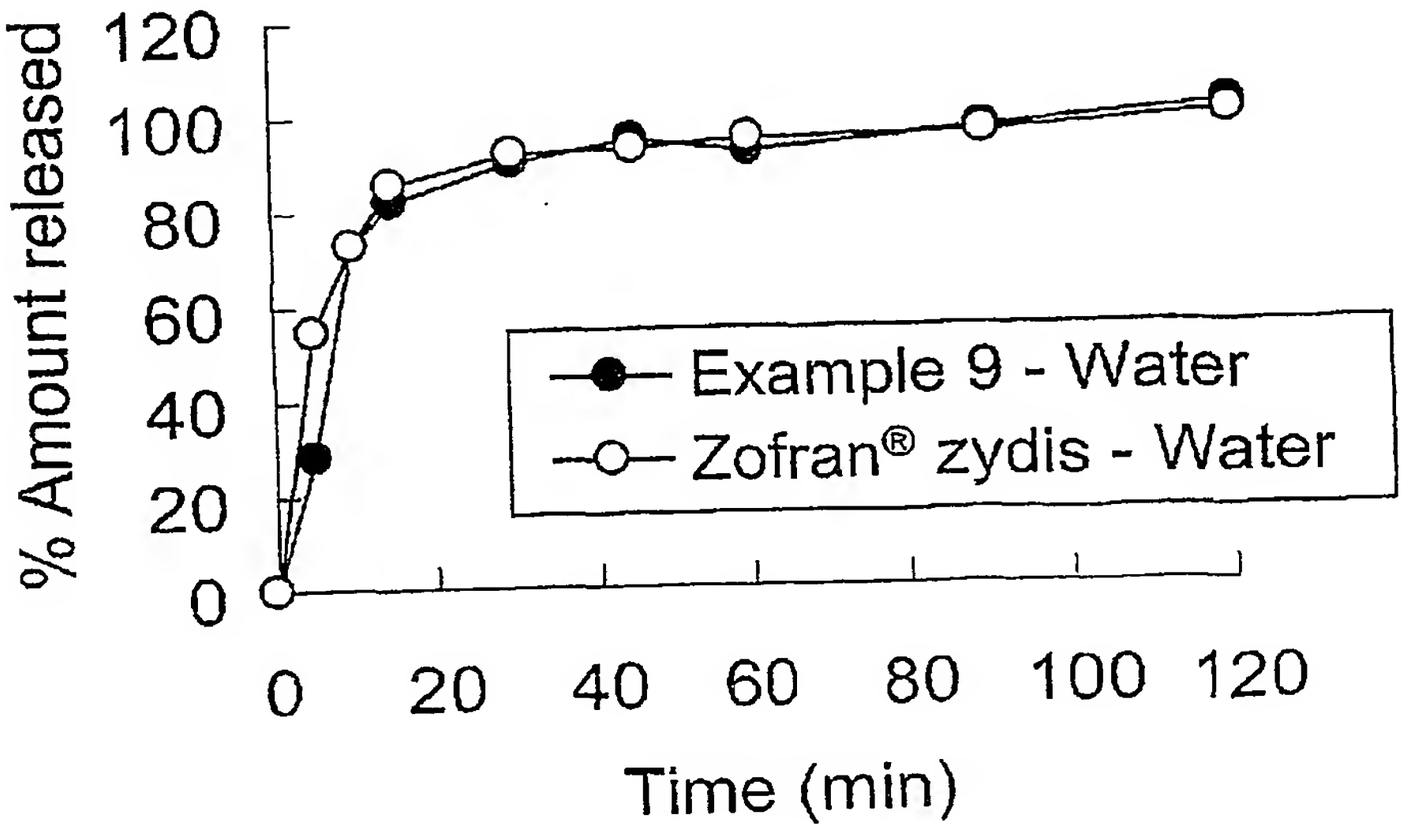

% Amount released
120
100
80
60
40
20
0
0
15
30
45
60
Time (min)
Example 9 - pH 6.8
Zofran® zydis - pH 6.8

Fig. 1D


% Amount released
120
100
80
60
40
20
0
0
20
40
60
80
100
120
Time (min)
Example 9 - Water
Zofran® zydis - Water

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR01/00893

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 9/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)

CA Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Koezumi et al., "New method of preparing high-porosity rapidly saliva-soluble compressed talbets using mannitol with camphor, a subliming materical" in Int. J. Pharm. (1997), 152(1) pages 127-131. see entire document.	1-20
A	US 6024891 A (CIMA LABS INC.) 15. February 2000 (15. 02. 2000). see abstract, examples 1-8 and claims 1-40, cited in the application.	1-20
A	US 4134943 A (BOEHRINGER MANNHEIM GBMH) 16. January 1979 (16. 01. 1979) see entire document, cited in the application.	1-20

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevence

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 SEPTEMBER 2001 (11.09.2001)	12 SEPTEMBER 2001 (12.09.2001)
Name and mailing address of the ISA/KR Korean Intellectual Property Office Government Complex-Daejeon, Dunsan-dong, Seo-gu, Daejeon Metropolitan City 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer Yoon, Kyung Ae Telephone No. 82-42-481-5609

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